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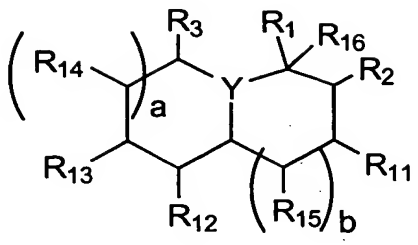
CLAIMS

1. A compound of Formula (IA):



(IA)

wherein:

a is 0 and b is 0;

or a is 1 and b is 0;

or a is 1 and b is 1;

Y is selected from N and N→O;

one of R_1, R_2 and R_3 is a ring moiety selected from C_{4-6} cycloalkyl, phenyl, naphthyl, C_{1-5} heterocyclyl, (C_{4-6} cycloalkyl)C_{1-3} alkylene, (phenyl)C_{1-3} alkylene, (naphthyl) C_{1-3} alkylene, and (C_{1-5} heterocyclyl)C_{1-3} alkylene;

and the remaining two of R_1, R_2 and R_3 are independently selected from hydrogen, halogen, and C_{1-6} alkyl;

wherein said ring moiety is substituted with a moiety of formula:

-X-W-Z, X-Z, W-Z or Z;

wherein X is selected from the group consisting of O, S, SO_2, SO, NR_4, -CH=CH-, —C≡C—, -OCH_2-C≡C-, -C≡C-CH_2O-, -$CH(R_5)$-, CO, -O-CO-, -CO-O-, CHOH, -NR_4-CO-, -CO-NR_4-, -SO_2-NH-, -NR_4-SO_2-, and -SO_2-NR_4-; R_4 is H, or C_{1-6} alkyl; R_5 is H, C_{1-6} alkyl, or hydroxy;

W is C_{1-6} alkylene, phenylene, (phenylene)(C_{1-3} alkylene), or -CH_2-CHCH-CH_2-;

Z is selected from:

(i) $NR_{21}R_{22}$, $NHCOR_{23}$, or $NHSO_2R_{23}$,

(ii) C_{3-6} heterocyclyl or C_{7-12} fused bicyclyl, and

(iii) phenyl substituted with a C_{3-6} heterocyclyl group, or with a (C_{3-6} heterocyclyl)C_{1-6} alkylene group,

wherein each phenyl or heterocyclyl group in (ii) or (iii) may be substituted with one to four substituents independently selected from the group consisting of halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyclohexyl, cyclohexenyl, phenyl, (phenyl)C_{1-6} alkylene, trihalo C_{1-6} alkyl, nitro, SCH_3, $NR_{21}R_{22}$, amido, amidino, amino C_{1-6} alkyl, acetylene, $CHR_{23}R_{24}$, COR_{23}, acetyl, $NHCOCH_3$, C_{3-6} heterocyclyl, (C_{3-6} heterocyclyl) C_{1-6} alkylene, cyano, $NHSO_2CH_3$, $N(SO_2CH_3)_2$, carboxy, C_{1-6} alkoxycarbonyl, amidoxime, trihalo C_{1-6} alkoxy, oxo, hydroxyiminomethyl, C_{1-6} alkylcarboxy, carboxy C_{1-6} alkyl, trihaloacetyl, and methylsulfonyl;

wherein each of R_{21} and R_{22} is independently selected from H, C_{1-6} alkyl, C_{4-7} cycloalkyl, phenyl, benzyl, C_{1-6} alkoxy, hydroxy, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-8} acyl, C_{1-8} alkylsulfonyl;

R_{23} is C_{1-6} alkyl, C_{4-7} cycloalkyl, phenyl, benzyl, C_{1-6} alkoxy, hydroxy, aryl, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-8} acyl, C_{1-8} alkylsulfonyl;

R_{24} is H, halogen, hydroxy, amino, C_{1-6} alkyl, C_{4-7} cycloalkyl, phenyl, or benzyl;

in addition, said R_1, R_2 or R_3 that is a ring moiety is optionally substituted with between 1 and 3 substituents Q_1, Q_2, and Q_3, which, if present, are independently selected from: R_{25}, $NR_{26}R_{27}$, $NHCOR_{28}$, $NHSOR_{29}$, and $NHSO_2R_{30}$;

wherein R_{25} is H, C_{1-6} alkyl, C_{4-7} cycloalkyl, phenyl, benzyl, C_{1-6} alkoxy, hydroxy, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-8} acyl, or C_{1-8} alkylsulfonyl;

wherein each of R_{26} and R_{27} is independently selected from H, C_{1-6} alkyl, C_{4-7} cycloalkyl, phenyl, benzyl, C_{1-6} alkoxy, hydroxy, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-8} acyl, C_{1-8} alkylsulfonyl;

each of R_{28}, R_{29}, and R_{30} is C_{1-6} alkyl, C_{4-7} cycloalkyl, phenyl, benzyl, C_{1-6} alkoxy, hydroxy, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-8} acyl, C_{1-8} alkylsulfonyl;

and

R_{11}, R_{12}, R_{14} and R_{15} are each independently selected from hydrogen, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

R_{13} is selected from hydrogen, oxo, and phenyl;

R_{16} is selected from hydrogen, cyano, C_{1-6} alkyl, and C_{1-6} alkylamino;

wherein each of the above carbocyclyl and heterocarbocyclyls can be optionally substituted with between 1 and 3 substituents selected from C_{1-4} alkyl, hydroxy, amino, halo, C_{1-4} alkoxy, $CONH_2$, phenyl, and C_{1-4} alkylamino, di(C_{1-4})alkylamino;

and wherein –X-W-Z is not [4-(imidazol-1yl)-phenyl]oxy where a is 1 and b is 0;

or a pharmaceutically acceptable salt, ester, or amide thereof.

2. The compound of claim 1, wherein Y is N.

3. The compound of claim 1, wherein a is 1 and b is 0.

4. The compound of claim 1, wherein a is 0 and b is 0.

5. The compound of claim 1, wherein a is 1 and b is 1.

6. The compound of claim 1, wherein at least two of R_{11}, R_{12}, R_{13}, and R_{16} are H.

7. The compound of claim 1, wherein, if present, R_{14} and R_{15} are H.

8. The compound of claim 1, wherein one of R_1 and R_2 is a substituted ring.

9. The compound of claim 1, wherein R_1 is a substituted ring.

10. The compound of claim 1, wherein R_2 is a substituted ring.

11. The compound of claim 1, wherein one of R_1 and R_2 is a substituted phenyl or substituted pyridyl; and the other two of R_1, R_2 and R_3 are independently selected from hydrogen, halogen, and C_{1-6} alkyl; wherein the substituent on said substituted phenyl or pyridyl is a para- or meta- substituent.

12. The compound of claim 1, wherein the substituent on said ring is of formula: X-Z or X-(C_{1-6} alkylene)-Z, wherein X is selected from the group consisting of of O, S, NR_{21}, $-OCH_2-C\equiv C-$, $-NR_{21}-CO-$, $-CO-NR_{21}-$, $-NH-SO_2-$, $-SO_2-NH-$, $-NR_{23}-SO_2-$, and $-SO_2-NR_{23}$; and Z is selected from (i) $NR_{21}R_{22}$ and pyridyl, piperidyl, and pyrrolidyl, optionally substituted.

13. The compound of claim 1, wherein a is 1 and b is 0; Y is N; one of R_1 and R_2 is phenyl para-substituted with X-W-Z, wherein X is O, NH, N(C_{1-3} alkyl), NHCO, $NHSO_2$, or S; and W is C_{2-5} alkylene.

14. The compound of claim 13, wherein Z is piperidyl or pyrrolidyl, optionally substituted with methyl, $CONH_2$, or phenyl.

15. The compound of claim 14, wherein R_{11}, R_{12}, R_{13}, and R_3 are each H.

16. The compound of claim 1, wherein each of R_3, R_{11}, R_{12}, and R_{13} is H, halo, methyl, or methoxy.

17. The compound of claim 1, wherein the R_1, R_2, or R_3 that is a ring moiety is substituted with a moiety of formula –X-W-Z, -X-Z, or –W-Z.

18. The compound of claim 1, selected from
(S, S)-3-(4-(3-Piperidinylpropoxy)phenyl)octahydroindolizine;
(R, R)-3-(4-(3-Piperidinylpropoxy)phenyl)octahydroindolizine;

trans-3-(4-(3-Piperidinylpropoxy)phenyl)octahydroindolizine;
anti-2-(4-(3-Piperidinylpropoxy)phenyl)octahydroindolizine;
syn-2-[4-(3-Piperidinylpropanoxy)phenyl]octahydroindolizine;
3-[4-(Piperidinylpropoxy)phenyl]hexahydro-1H-pyrrolizine;
5-[4-(4-Piperidinylbutoxy)phenyl]indolizine;
trans-3-[4-(N-5-Piperidylpentylamino)phenyl]octahydroindolizine;
5-[4-(3-Piperidinylpropoxy)phenyl]octahydroindolizine;
5-[4-(4-Piperidinylpentanoxy)phenyl]octahydroindolizine;
N-Methyl-N-[4-(*trans*-Octahydro-3-indolizinyl)phenyl]-3-piperidinylpropenamide;
trans-3-[4-(*N*-3-Piperidylpropylamino)phenyl]octahydroindolizine; *trans*-3-[4-(3-Piperidinylmethylpropargyloxy)phenyl]octahydroindolizine;
trans-3-[4-(*N*-5-Piperidylpentanamido)phenyl]octahydroindolizine;
trans-3-{4-[2,2'-(*N*-Methylpyrrolidinyl)ethoxy]phenyl}octahydroindolizine;
anti-2-[3-(3-Piperidinylpropyloxy)phenyl]octahydroindolizine;
trans-3-[4-(N-4-Piperidylbutanamido)phenyl]octahydroindolizine;
trans-3-[4-(*N*-Methyl-*N*-3-piperidylpropylamino)phenyl]octahydroindolizine;
trans-3-[4-(3-Piperidylsulfonylamino)phenyl]octahydroindolizine;
5-[4-(2-Piperidinylethanoxy)phenyl]octahydroindolizine;
trans-3-{4-[2,2'-(*N*-Methylpiperidinyl)ethoxy]phenyl}octahydroindolizine;
tran-3-[4-(4-Methylaminophenylthio)phenyl]octahydroindolizine;
trans-3-[4-(N-Methyl-*N*-5-piperidylpentylamino)phenyl]octahydroindolizine;
3-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-octahydro-indolizine;
Dimethyl-{3-[4-(octahydro-indolizin-3-yl)-phenoxy]-propyl}-amine;
trans-3-[4-(N-3-Piperidinylpropanamido)phenyl]octahydroindolizine;
trans-3-{4-[(2-Piperidylethyl)sulfonyl]amidophenyl}octahydroindolizine;
trans-3-{4-[(2-Piperidylethyl)sulfonyl-N-methylamino]phenyl}octahydroindolizine; and
tran-3-[4-(4-Carboxylicphenylthio)phenyl]octahydroindolizine.

19. The compound of claim 1, selected from:
trans-3-[4-((4-Amidoxime)phenylthio)phenyl]octahydroindolizine;
trans-3-[4-(4-Methansulfonaminophenoxy)phenyl]octahydroindolizine;
trans-3-{4-[2,2'-(*N*-Trifluoroethylpiperidinyl)ethoxy]phenyl}octahydroindolizine;

trans-3-{4-[2,2'-(1-*tert*-Butylcarboxylatepiperidinyl)ethoxy]phenyl}-octahydroindolizine;
trans-3-[4-(3-Piperidylsulfonyl-N-methylamino)phenyl]octahydroindolizine;
trans-3-[4-(4-Aminophenylthio)phenyl]octahydroindolizine;
trans-3-[4-(*N*-Methyl-N-5-piperidylpentanamido)phenyl]octahydroindolizine;
Octahydro-3-[4-(4-pyridinylthio)phenyl]indolizine;
trans-3-[4-(*N*-Phenyl-1-piperazinylmethyl)phenyl]octahydroindolizine;
trans-3-[4-(4-Pyridinylethenyl)phenyl]octahydroindolizine;
trans-3-{4-[2,2'-(*N*-Trifluoroacetylpiperidinyl)ethoxy]phenyl}octahydroindolizine;
tran-3-[4-(3-(2-Dimethylaminoethyl)amino)phenyl]octahydroindolizine;
trans-3-[4-(4-Pyridyloxy)phenyl]octahydroindolizine;
trans-3-{4-[2,2'-(*N*-Amidinopiperidinyl)ethoxy]phenyl}octahydroindolizine;
trans-3-[4-(4-Pyridylmethan-1-ol)phenyl]octahydroindolizine;
trans-3-[4-(2,2'-piperidinylethoxy)phenyl]octahydroindolizine;
4-[4-(Octahydro-indolizin-3-yl)-phenoxy]-quinazoline;
trans-3-[4-(N-Methylsulfonyl)piperidinylamino)phenyl]octahydroindolizine;
trans-3-[4-(3-bis-Methansulfonaminobenzyloxy)phenyl]octahydroindolizine;
3-(4-Thiophen-2-yl-phenyl)-octahydro-indolizine;
trans-3-[4-(*N*-Methylsulfonyl-4-aminopiperidine)phenyl]octahydroindolizine;
4-[4-(4-Pyridylthio)phenyl]octahydoquinolizine;
trans-3-[4-(3-Methansulfonaminobenzyloxy)phenyl]octahydroindolizine; and
trans-3-[4-(4-Trifluromethoxyphenyl)phenyl]octahydroindolizine .

20. The compound of claim 1, selected from:
3-Biphenyl-4-yl-octahydro-indolizine;
trans-3-(4-Phenoxy-phenyl)-octahydro-indolizine;
cis-3-(4-Phenoxy-phenyl)-octahydro-indolizine;
Dimethyl-[5-(octahydro-indolizin-3-yl)-naphthalen-1-yl]-amine;
[4-(Octahydro-indolizin-3-yl)-phenyl]-diphenyl-amine;
5-[4-(4-Pyridinylthio)phenyl]octahydroindolizine;
5-[4-(4-Nitrophenylthio)phenyl]octahydroindolizine;
3-[4-(Pyridin-3-yloxy)-phenyl]-octahydro-indolizine;
2-[4-(Octahydro-indolizin-3-yl)-phenoxy]-1H-benzoimidazole;

3-[4-(4-Nitro-phenylsulfanyl)-phenyl]-octahydro-indolizine;
3-[4-(Pyrimidin-2-ylsulfanyl)-phenyl]-octahydro-indolizine;
2-[4-(Octahydro-indolizin-3-yl)-phenylsulfanyl]-3H-quinazolin-4-one;
2-[4-(Octahydro-indolizin-3-yl)-phenoxy]-quinoline;
2-Methyl-8-[4-(octahydro-indolizin-3-yl)-phenoxy]-quinoline;
4-[4-(Octahydro-indolizin-3-yl)-phenylsulfanyl]-benzonitrile;
5-(4-(4-Aminophenylthio)phenyl)octahydroindolizine;
3-Methylamino-3-(4-bromophenyl)octahydroindolizine;
trans-3-[4-(4-Methylene-1,3-thiazolidine-2,4-diimine)phenyl]octahydroindolizine;
4'-(Octahydro-indolizin-3-yl)-biphenyl-3-ylamine;
3-(4-Thiophen-3-yl-phenyl)-octahydro-indolizine;
2-[4-(Octahydro-indolizin-3-yl)-phenyl]-thiophene-3-carbaldehyde;
4'-(Octahydro-indolizin-3-yl)-biphenyl-4-carbaldehyde;
3-(4'-Fluoro-biphenyl-4-yl)-octahydro-indolizine; and
trans-3-[4-(3-hydroxyiminomethylthienyl)phenyl]octahydroindolizine.

21. The compound of claim 1, selected from:
trans-3-[4-(3-Methylsulfonylaminophenyl)phenyl]octahydroindolizine;
anti-2-[2-(3-Piperidinylpropoxy)phenyl]octahydroindolizine;
trans-3-[4-(4-Aminophenoxy)phenyl]octahydroindolizine;
trans-3-(4-Aminophenyl)octahydroindolizine;
trans-3-(4-(N,N-Dimethylamino)phenyl)octahydroindolizine;
trans-3-(4-(Methylsulfonylamino)phenyl)octahydroindolizine;
trans-3-(4-(bis-Methylsulfonylamino)phenyl)octahydroindolizine;
trans-3-{4-[4-(*N*-(1,1-dimethylethoxycarbonyl)piperidinylamino]phenyl}octahydroindolizine;
trans-3-[4-(4-Piperidinylamino)phenyl]octahydroindolizine;
trans-3-[4-(*N*-Ethyl-N-4-N-methylsufonylpiperidinylamino)phenyl]octahydroindolizine;
N-[4-(*trans*-Octahydro-3-indolizinyl)phenyl]propenamide;
N-Methyl-N-[4-(*trans*-Octahydro-3-indolizinyl)phenyl]propenamide; and
trans-3-{4-[(2-Pyrrolidylethyl)sulfonylamino]phenyl}octahydroindolizine.

22. The compound of claim 1, selected from:
trans-3-{4-[(4-Chlorophenyl)methan-1-ol]phenyl}octahydroindolizine;
trans-3-{4-[(4-Chlorobenzyl]phenyl}octahydroindolizine;
[4-(Octahydro-indolizin-3-yl)-phenyl]-pyridin-3-ylmethyl-amine;
[4-(Octahydro-indolizin-3-yl)-phenyl]-pyridin-2-ylmethyl-amine;
[4-(Octahydro-indolizin-3-yl)-phenyl]-thiophen-3-ylmethyl-amine;
Furan-2-ylmethyl-[4-(octahydro-indolizin-3-yl)-phenyl]-amine;
[4-(Octahydro-indolizin-3-yl)-phenyl]-pyridin-4-ylmethyl-amine;
Benzyl-[4-(octahydro-indolizin-3-yl)-phenyl]-amine;
[4-(Octahydro-indolizin-3-yl)-phenyl]-(1-oxy-pyridin-4-ylmethyl)-amine;
(1H-Imidazol-2-ylmethyl)-[4-(octahydro-indolizin-3-yl)-phenyl]-amine;
Dibenzyl-[4-(octahydro-indolizin-3-yl)-phenyl]-amine;
(*R, R*)-Octahydro-3-[4-(4-pyridinylthio)phenyl]indolizine; and
(*S, S*)-Octahydro-3-[4-(4-pyridinylthio)phenyl]indolizine. .

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 1, 13, 14 or 19.

24. A method for treating a disorder or condition mediated by the histamine H_3 receptor in a subject, said method comprising administering to a subject a therapeutically effective amount of a compound of claim 1, 13 or 19.

25. A method of claim 24, wherein said disorder or condition is selected from the group consisting of sleep/wake disorders, arousal/vigilance disorders, migraine, asthma, dementia, mild cognitive impairment (pre-dementia), Alzheimer's disease, epilepsy, narcolepsy, eating disorders, motion sickness, vertigo, attention deficit hyperactivity disorders, learning disorders, memory retention disorders, schizophrenia, nasal congestion, allergic rhinitis, and upper airway allergic response.

26. A method for treating a disease or condition modulated by at least one receptor selected from the histamine H_1 receptor and the histamine H_3 receptor, said method comprising (a) administering to a subject a jointly

effective amount of a histamine H_1 receptor antagonist compound, and (b) administering to the subject a jointly effective amount of a compound of claim 1, 13, 14, or 19, said method providing a jointly therapeutically effective amount of said compounds.

27. The method of claim 25 wherein the histamine H_1 receptor antagonist and the compound of claim 1, 13, 14, or 19 are present in the same dosage form.

28. A method for treating diseases or conditions modulated by at least one receptor selected from the histamine H_2 receptor and the histamine H_3 receptor in a subject, comprising (a) administering to the subject a jointly effective amount of a histamine H_2 receptor antagonist compound, and (b) administering to the subject a jointly effective amount of a compound of claim 1, 13, 14, 19, said method providing a jointly therapeutically effective amount of said compounds.

29. The method of claim 27 wherein the histamine H_2 receptor antagonist and the compound of claim 1 are present in the same dosage form.

30. A method for treating one or more disorders or conditions selected from the group consisting of sleep/wake disorders, narcolepsy, and arousal/vigilance disorders, comprising administering to a subject a therapeutically effective amount of a compound of claim 1, 13, 14, or 19.

31. A method for treating attention deficit hyperactivity disorders (ADHD), comprising administering to a subject a therapeutically effective amount of a compound of claim 1, 13, 14, or 19.

32. A method for treating one or more disorders or conditions selected from the group consisting of dementia, mild cognitive impairment (pre-dementia), cognitive dysfunction, schizophrenia, depression, manic disorders, bipolar disorders, and learning and memory disorders, comprising administering to a

subject a therapeutically effective amount of a compound of claim 1, 13, 14, or 19.

33. A method for treating or preventing upper airway allergic response, nasal congestion, or allergic rhinitis, comprising administering to a subject a therapeutically effective amount of a compound of claim 1, 13, 14, or 19.

34. A method for studying disorders mediated by the histamine H_3 receptor, comprising using an "C- or ^{18}F-labeled compound of claim 1 or 19 as a positron emission tomography (PET) molecular probe.